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## NOVEL SYNTHETIC APPROACHES BASED ON DMAP-CATALYZED ACYLATIONS OF ORGANIC NITROGEN COMPOUNDS

*Some new reactions of preparative interest dealing with amines, urethans and amides, resulting in novel structures, are reviewed. The key step in most cases is the introduction of the *t*-butoxycarbonyl (Boc) group using  $\text{Boc}_2\text{O}$  under anhydrous conditions and 4-dimethylaminopyridine as a catalyst. Apart from functioning as a protecting group, Boc confers quite useful properties to some of the new derivatives. Among the applications are simple procedures for the removal of protecting groups of acyl type and for selective protection of mixed primary/secondary polyamines. A convenient synthesis of  $\text{Boc}_2\text{NH}$ , a useful Gabriel reagent, is also described.*

## INTRODUCTION

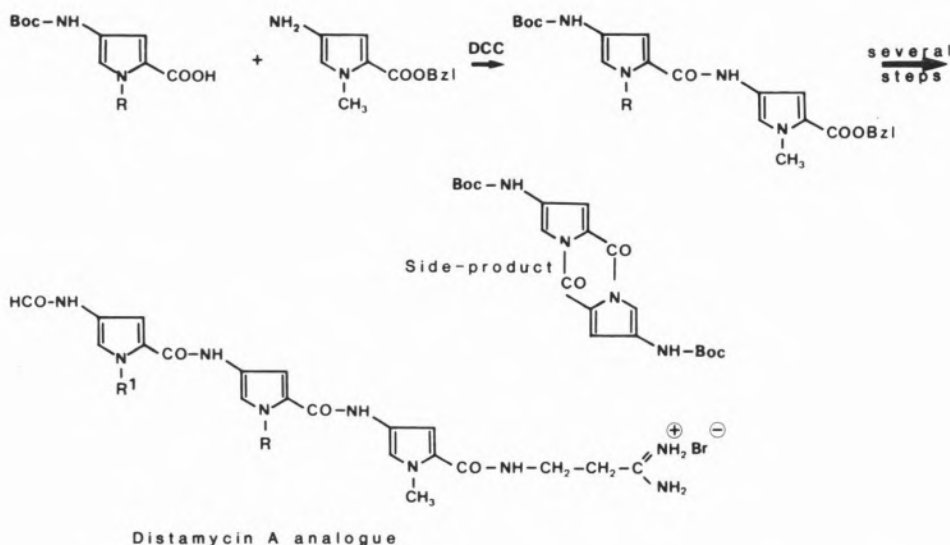
This paper reviews some new reactions of preparative interest dealing with pyrroles, indoles, amides, urethans, peptides and amines. The key step in all cases is the introduction of the *t*-butoxycarbonyl (Boc) group with  $\text{Boc}_2\text{O}$  under anhydrous conditions in the presence of catalytic amounts of 4-dimethylaminopyridine (DMAP). In the pyrrole and indole cases Boc serves as a conventional protecting group, but for the remaining types of compounds mentioned its introduction gives rise to additional new synthetic options. This conversion of amides to the corresponding Boc-acylamides thus renders their original carbonyls extremely susceptible to attack by nucleophiles, which can be exploited for selective amide cleavage, simultaneously providing Boc-protected amino components. A useful application of urethan NH-substitution is illustrated in a new convenient synthesis of  $\text{Boc}_2\text{NH}$ , an alternative Gabriel reagent. The potential usefulness of peptide bond protection is demonstrated under conditions known to give rise to peptide oxazolone formation with concomitant racemization. Boc-substitution excludes this undesired side reaction and its consequences. Finally a strategy discriminating between primary and secondary amino groups is discussed. This novel approach offers promising possibilities to accomplish selective modifications of polyamine derivatives.

DMAP is a powerful acylation catalyst. [1,2] In this paper some novel applications based on its use, related to simple nitrogen compounds, will be presented and discussed with particular reference to their synthetic utility. As in most previous work of this type, the reaction conditions in these new applications are mild and the experimental set-up is simple. Since in addition, the yields of product were generally high, the new applications appear to be attractive from the synthetic point of view.

## APPLICATIONS

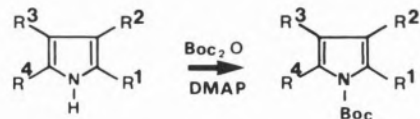
*Protection of the pyrrole and indole nitrogen.*

— In connection with synthetic work in the distamycin A field, [3] we noticed that in one step involving a pyrrole-2-carboxylic acid with an unsubstituted nitrogen function, the product was obtained in a low yield and a side-product was formed:



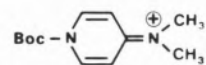
To eliminate this side-product we considered the possibility of using a protecting group for the pyrrole nitrogen, such as Boc, first described by Carpino [4] and briefly afterwards by others. [5,6] Inspection of the literature revealed that 1-Boc-pyrrole had been prepared previously only by using a strong base. [7] For the corresponding acetylated compound a mild procedure was found, [8] involving reaction with acetic anhydride under weakly basic conditions in the presence of DMAP. When we replaced acetic anhydride with di-*t*-butyl dicarbonate ( $\text{Boc}_2\text{O}$ ) and applied similar conditions with a series of pyrroles and indoles, the corresponding 1-Boc-derivatives were obtained under surprisingly mild conditions (slight excess of  $\text{Boc}_2\text{O}$  and 0.05-0.1 equiv. of DMAP, gene-

rally in acetonitrile, at room temperature for a few hours) in excellent yields. [9]



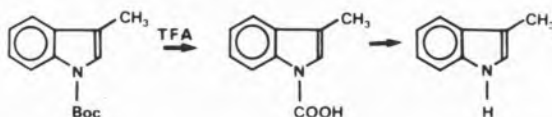
As to the mechanism of the reaction, we can point out that a Boc-DMAP adduct has been

isolated as its tetrafluoroborate, [10] most probably stabilized by resonance:



Since 1-Boc-pyrrole-2-carboxylic acids can no longer give rise to a side-product like the one mentioned above, we could subsequently prepare further distamycin A analogues in much higher yields than previously. [11] Our procedure was later also applied by others in the synthesis of antitumour substances containing pyrrole and indole rings. [12,13] The amino acid tryptophan is sensitive to various reagents used in the synthesis of peptides. [14] Particularly acidolytic cleavage of acid-labile protecting groups is often accompanied by significant formation of side-

products. This is obviously due to the enhanced reactivity of the electron-excessive indole moiety toward various carbonium ions formed during deprotection. [15] Although many investigators seem to prefer to work with unprotected indole nitrogens, an increasing number have begun to use the N<sup>in</sup>-formyl group. [16] We therefore decided to attempt to protect the indole nitrogen of tryptophan with Boc. Its introduction could be accomplished using the conditions mentioned in the previous paragraph. Using N<sup>α</sup>-Boc-Trp (Boc)-OMe as a model substance, we found that with HCl in dioxan the N<sup>α</sup>-Boc could be cleaved off selectively, whereas trifluoroacetic acid (TFA) removed both Boc-groups. [17] Obviously, on the indole nitrogen the reaction took place in two steps, [9,18] as illustrated for 1-Boc-3-methylindole: [9]



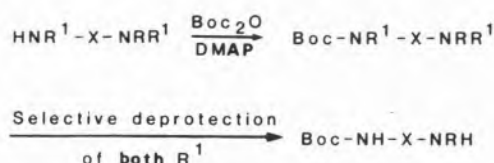
TFA thus cleaves off the *t*-butyl group rapidly. The intermediate 1-COOH derivative is considerably more stable under these conditions, but is converted to the corresponding indole during aqueous workup. Conceivably, the 1-COOH serves as the effective protective group during the anhydrous deprotection step by blocking the nitrogen and deactivating the indole nucleus.

To further prove the usefulness of Boc as an indole and tryptophan protecting group, a tetrapeptide containing two tryptophan residues was synthesized. [17] More recently, this procedure has also been used in the synthesis of an <sup>11</sup>C-labelled substance P analogue also containing two tryptophan residues. [19]

#### Reactions of urethans, amides and peptides.

— During our tryptophan work we noticed that with increasing amounts of Boc<sub>2</sub>O we got less pure products. Spectral evidence indicated attack on urethan nitrogens. Therefore,

we decided to study the reactivity of some simple urethans such as Boc-Gly-OBzl under this set of conditions. To our surprise we found that the latter compound was converted quantitatively to Boc<sub>2</sub>-Gly-OBzl in which both hydrogens of the amino group had been replaced by *t*-butoxycarbonyl groups. [20] This was a rather unexpected finding, particularly considering the widespread use of this protecting group in the field of peptide synthesis and all the methods [14] developed in this context for its introduction without detecting a Boc<sub>2</sub>-derivative.



Further experiments with other model compounds made it evident that not only urethans but also amide and peptide nitrogens are attacked by the Boc-DMAP adduct. In a primary amide, both hydrogens could be substituted with Boc groups. [20] Independently of our work, Grieco *et al.* [21] observed that secondary amides and lactams reacted in this way.

A large set of typical secondary acylamides were next reacted similarly and, with one exception, gave rise to the corresponding Boc-amide. [22] The exception was pivalanilide, whose bulkiness completely prevented acylation on nitrogen. Although in a few other cases an influence of steric effects on the reaction rate was noticed, the reaction could always be brought to completion with additional Boc<sub>2</sub>O and/or longer reaction time. Due to the bulkiness of the reagent and its adduct with DMAP, [1,2] steric hindrance might prevent reaction in some cases. Returning to the amides, however, we were able to demonstrate that not only carboxamides could be reacted in this way but also a phosphin-, a sulfen- and a sulfonamide underwent reaction under the same condi-

tions. [22] The product originating from the last-mentioned reaction will be further discussed below.

*Cleavage of amides.* — Amides are often regarded as quite stable compounds, which require heating with strong acid or base for cleavage. [23] Although a few milder, selective cleavage methods have been developed, such as those for *o*-hydroxy- and *o*-aminoanilides which leave  $\beta$ -lactam functions present in the same molecule intact, each of these methods is rather narrowly limited in scope. [24]

Grieco *et al.* [21] were the first to show that Boc-amides and lactams could be hydrolyzed easily with lithium hydroxide at room temperature or methanolized with methoxide in methanol at 0 °C. We made Boc-derivatives of simple formamides, acetamides and benzamides and demonstrated that all of them could be converted to *t*-butyl carbamates by mild aminolysis, thus offering a new possibility for removal of these three nitrogen protecting groups. [25] The more labile formyl group could even be removed by the weak base morpholine at room temperature. In our preparative experiments we preferred to use diethylaminoethylamine (DEAEA) for aminolysis because that afforded a particularly simple and efficient work-up procedure afterwards. The Boc-derivatives of all secondary carboxamides tried could be cleaved under these mild conditions. [26] They also seemed to be cleaved very efficiently by methanolysis using tetramethylguanidine (TMG) in methanol. [26]

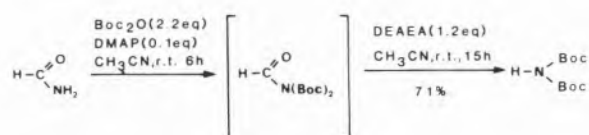


As pointed out in a previous paragraph, the Boc-derivative of tosylanilide could also be prepared. [22] Maia *et al.* [27] recently discovered that the presence of the Boc-group significantly lowered the voltage required for

electrochemical removal of the tosyl group. Some results are presented in a poster at this symposium.

*Synthesis and use of di-*t*-butyl iminodicarbonate, an alternative Gabriel reagent.* —

Di-*t*-butyl iminodicarbonate was first prepared by a Curtius rearrangement of the acyl azide derived from *t*-butyl oxalylhydrazide followed by reaction with *t*-butanol. [28] Later, a more convenient procedure based on oxidation with  $\text{Pb}(\text{OAc})_4$  in butanol of easily prepared *t*-butyl oxamate was developed. [29] The substance is of considerable interest as an alternative Gabriel reagent [30] because of the very mild conditions required in this case to liberate the amine obtained afterwards. Using the methodology outlined in previous paragraphs, we were recently able to develop a simple one-pot procedure for the synthesis of di-*t*-butyl iminodicarbonate on a large scale. [31] As a starting material we chose formamide which, as a primary amide, was converted first to the corresponding di-Boc derivative. [20] This compound was then directly aminolysed with DEAEA to give the product in 71% yield after recrystallization. Like phthalimide, this substance gives a stable potassium salt suitable for alkylation reactions.



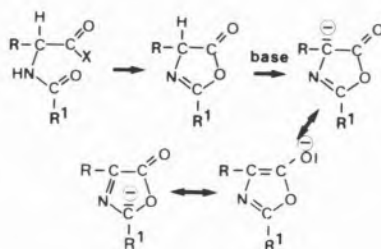
Boc = *t*-butoxycarbonyl

DEAEA = 2-diethylaminoethylamine

DMAP = 4-dimethylaminopyridine

We reacted the potassium salt with benzyl chloride and obtained Boc<sub>2</sub>-benzylamine identical with material by an alternative method. [22] Commercial chloromethylated polystyrene reacted correspondingly. Amino-methyl polystyrene [32,33] is of interest in various contexts. [33] Particularly, it serves as starting material in the phenylacetamidomethyl (Pam) approach [34] to solid phase peptide synthesis.

*A new approach to reduced racemization in fragment condensation of peptides.* — Although the factors involved in peptide racemization have been rather well studied and several available methods for the synthesis of peptides can be considered safe in this respect, racemization repeatedly presents problems to every practitioner of peptide synthesis. This is particularly the case when peptide fragments are condensed into larger molecules. The activation of the carboxyl group which is intended to form the new peptide bond sometimes leads to oxazolone formation. In the presence of base proton abstraction can then occur at the  $\alpha$ -carbon involved, thus resulting in partial loss of chirality. [14]



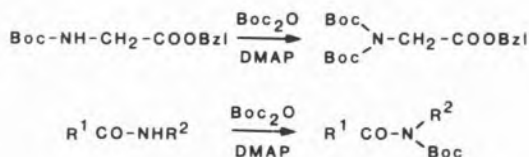
Using a model peptide in which peptide oxazolone formation was excluded by protection of the corresponding peptide bond as described in a previous paragraph, we recently decided to challenge the current conception in this field. [35] In parallel experiments, amino-protected Gly-Phe with and without a Boc group on the peptide bond were coupled with the same Phe ester using various conditions known to give rise to peptide racemization under normal conditions. After treatment with acid to remove all protecting groups, the diastereomeric tripeptides were separated by high performance liquid chromatography and the D,L/L,L ratio was determined. Whereas these ratios varied between 16 and 38% in the reference experiments, in all cases where a Boc group was present on the Gly-Phe peptide bond the corresponding values were well below 1%. Whether these minute amounts were due to racemization by an alternative mechanism or simply to opti-

cally impure precursors remains to be determined. Nevertheless, it demonstrates that protection of peptide bonds can be potentially useful.

*Selective protection of mixed primary/secondary di- and polyamines.* — Finally, some preliminary studies in the field of di- and polyamines will be discussed briefly. [36] Basically, these illustrate the preparative usefulness of the principles described above with another class of biologically important compounds. [37]

Many polyamines, such as spermidine and spermine, contain both primary and secondary amino groups. Nonsymmetrical molecules of this type present an additional challenge when one attempts to accomplish selective modifications at the various amino groups. For selective protection of spermidine and its homologues some special methods have been developed, [38] but to our knowledge no general methods for selective protection of mixed primary/secondary amines are presently available.

Having found that amides and urethans containing a hydrogen atom on their nitrogens could be converted to Boc-derivatives, we began to explore various synthetic approaches toward a general procedure in this context. In principle, any monofunctional amino protecting group  $R^1$ , orthogonal to Boc, can be used:



If, however,  $R^1$  is instead an acyl group such as formyl, acetyl or benzoyl, its facilitated removal from the nitrogen function carrying the Boc group will lead to a product of the type Boc-NH-X-NRR<sup>1</sup>, which with mild acid can be converted to NH<sub>2</sub>-X-NRR<sup>1</sup> with a free primary amino group.

So far we have investigated  $R^1$  = benzyloxy-carbonyl and removed it afterwards by

catalytic hydrogenolysis. The reaction sequence depicted above seemed to work both on aliphatic and aromatic mixed primary/secondary diamines. Further studies are in progress.

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## RESUMO

### Novos métodos de síntese baseados em acilações de compostos orgânicos de azoto, catalisadas por DMAP

São apresentadas novas reacções com aminas, uretanos e amidas com interesse em síntese. Na maior parte dos casos, o passo chave traduz-se na introdução do grupo t-butoxicarbonilo (Boc), usando  $\text{Boc}_2\text{O}$  em condições anidras e 4-dimetilaminopiridina como catalisador. Para além do efeito de protecção, o grupo Boc confere propriedades muito úteis a alguns dos novos derivados. Entre as aplicações destacam-se processos simples para a remoção de grupos de protecção do tipo acilo e para a protecção selectiva de poliaminas, contendo, simultaneamente, grupos amina primária e secundária. Descreve-se ainda um bom método de síntese de  $\text{Boc}_2\text{NH}$ , um reagente de Gabriel de grande utilidade.